[redacted]

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/648,123	08/25/00	STANTON V	030586.0009.

HM12/0829

ANITA L. MEIKLEJOHN, PH.D.
FISH & RICHARDSON
225 FRANKLIN STREET
BOSTON MA 02110-2804

EXAMINER	
WILDER,C	
ART UNIT	**PAPER NUMBER**
1655	7

DATE MAILED: 08/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/648,123	STANTON, V.
Examiner	**Art Unit**
CB Wilder	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 20, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above, claim(s) *15 and 16* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-14, the Cytochrome P450 gene and the T to C variance at nucleotide 732 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that the search for the 21 variances of the Cytochrome P450 gene listed in Table 3 is not burdensome because the variances are all within a single gene. Applicant argues that the search required would be similar to that required if one were claiming nucleic acid molecules having a certain percent of identity to a particular sequence. Applicant further argues that useful probes and useful methods of genetic analysis often include the use of two or more variances, thus prosecution will become unduly burdensome if each variance is the subject of a distinct patent application. This is not found persuasive for the reasons discussed in the prior Office Action of Paper No. 2. To reiterate, the different variances are unrelated because each variance differs in structure and effect from each other variance. Specifically, the chemical structure of any one variance is necessarily different from that of any other variance because where, for example, as listed in Table 3, the variance comprising a nucleic acid with an A to G substitution at position 1870 of the Cytochrome P450 gene is chemically and structurally different from the nucleic acid with a T to C substitution at position 732 of the Cytochrome P450 gene. Likewise, the different variances are unconnected to each in design, since they differ in structure. The variance are different in operation, since they act at different sites in the same gene to cause different effects. Thus, the specific requirement is that

the inventions are capable of separate use, which is clearly evident in this application regarding these variances both by the separate claiming and because each variance can be separately screened. Further, the searches of the different variances are not coextensive because each variance is not required or is necessary for the function of the each other variance. Hence, each variance is separately patentable over each other variance.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 10 and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid probe comprising a nucleic acid sequence 7 to 500 nucleotide bases in length that selectively binds to a nucleic acid sequence comprising at least one variance in a Cytochrome P-450 (CYP3A4) gene, it does not reasonably provide enablement for a nucleic acid sequence that selectively binds to a nucleic acid sequence comprising at least one variance listed in Table 3 of the CYP3A4 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The first paragraph of section 112 requires the

specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 UsPQ2d 1400, 1404 (Fed. Cir. 1988)). These factor include, but are not limited to:

I. Quality of Experimentation Necessary:

The claimed invention is drawn to a nucleic acid probe comprising a nucleic acid sequence 7 to 500 nucleotide bases in length that specifically binds under selective binding conditions to a nucleic acid sequence comprising at least one variance in a Cytochrome P-450 gene (CYP3A4) or a sequence complementary thereto or an RNA equivalent, wherein the at least one variance is listed in Table 3, e.g., a T to C substitution at position 732 of the CYP3A4 gene. The specification at page 11 states that the variance or variant forms or forms of a gene is/are associated with a specific response to a drug. The specification continues by stating that the frequency of a specific variance or variant form of the gene may correspond to the frequency of an efficacious response to administration of a drug. The specification however fails to provide objective evidence that the claimed variances as listed in Table 3 are associated or relevant to a drug response, especially the T to C variance at position 732 of the CYP3A4 gene. There is no indication from the Description or Examples provided that the claimed variances recited in Table 3 modulate or alter expression or activity of the encoded protein. Merely identifying nucleic acid changes in a gene involved in drug metabolism does not equate to the nucleic acid changes (variances) being associated with a drug

response. While the art teaches genetic polymorphism such as A to G substitution at position 290 of the CYP3A4 gene (*Sinnett et al. 6,183,963 B1),* and the following other variances of the CYP3A4 gene; A to G at position 816, G to C at position -9 of intron 4, , T to G at position +52 of intron 6, C to T to C at position 579 of exon 7, T to G, at position +34 of intron 7, G to A at position +12 of intron 10 and C to T at position -11 of intron 11 (*Lichter et al., WO 99/13106*), as being associated with altered drug metabolism and altered risk of a variety of cancers and probes for detecting those variances therein, there is no evidence provided from the specification given that the claimed variances as recited in Table 3, especially a T to C at position 732 of the CYP3A4 gene are capable of the same function as the variances recited in the cited art. In fact, there is no evidence in the specification, but speculation that the claimed variances are indeed functional. As to the quality of experimentation required, further research would be required to determined if the claimed variances as recited in Table 3, especially the T to C substitution at position 732 of the CYP3A4 gene are indicative of drug response.

II. Amount of Direction and Guidance and presence of Working Examples

The specification does not provide probes comprising the variances recited in Table 3 that bears a reasonable correlation to the entire scope of the claim. The examples beginning at page 161 does not discloses a relation between the variances identified in Table 3 and a drug response. As noted earlier there is no teaching in the Examples that suggest that the claimed variance are functional or that the claimed variances as recited in Table 3 are indicative of a drug response or drug action or altered protein activity. Therefore, the claimed invention provides insufficient guidance

and direction for one skilled in the art to determined the efficacy of a drug response using the claimed variances recited in Table 3.

IV. Relative skill of those in the art and predictability or unpredictability of the art

The level of skill in the art at the time the invention was made is very high, however, the level of unpredictability is also high as indicated by Sinnett et al. (*6,183,963, filed Oct. 1998*) which teach that until recently, no genetic variant had been reported that explains the interindividual variability in e.g., CYP3A4 gene activity (col. 6, lines 36-38). Sinnett et al. discloses one variance an A to G at position 290 of the CYP3A4 gene as being involved in CYP3A4 gene activity. Although certain relevant techniques useful to the claimed invention were known in the prior art, the prior art does not teach a probe comprising the variants as recited in Table 3, especially a T to a C at position 732 of the CYP3A4 gene.

For all the forgoing reasons, undue experimentation is necessary for one of skill in the art to obtain the claimed invention.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

5. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 1-14 are indefinite at the recitation of "sequence complementary thereto" because the term "complementary thereto" can mean a polynucleotide complementary to a small region of a given DNA or alternatively complementing the entire region with or without a variant sequence present. Accordingly, as written, it is impossible for one skilled in the art to determined the metes and bounds of the claims. It is suggested replacing "complementary thereto" to "fully complementary thereto" or some other language that is supported by the specification as originally filed.

Claim Rejections - 35 USC § 102(b)

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-5, 8, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (5, 474,796, December 1995). Regarding claims 1-5 and 10, Brennan teaches a nucleic acid probe array comprising nucleotide sequences comprising every possible permutation of a target nucleic acid wherein the nucleotide sequences are 10 nucleotides in length (col. 9, lines 48-55). Brennan further teach wherein the probes comprises a detectable label (col. 9, lines 59-60). Since the probe array comprises every possible permutation of a target nucleic acid sequence, the claimed variances as recited in Table 3 are inherent in the teaching of Brennan. The genes as recited in claim 1 are

also inherent in the '796 patent in the teaching of a target nucleic acid which encompasses any known or unknown nucleic acid sequence. Therefore, the claimed invention of claims 1-5, 8 and 10 are anticipated by the reference of Brennan.

Claim Rejections - 35 USC § 102(a)

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.

9. Claims 1-5, 8, 9, 11-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Lichter et al. (WO 99/13106, March 1999). Regarding claims 1-5 and 11-13, Lichter et al. teach a DNA nucleic acid sequence 15-100 nucleotides in length that specifically binds under selective conditions to a nucleic acid sequence comprising at least one variance in a gene of the Cytochrome P450 (CYP3A4) gene) or a sequence complementary thereto and/or isolated DNA nucleic acid sequence of 15-100 nucleotides in length comprising at least one variance of the CYP3A4 gene) (page 4, lines 21-25 and page 5, lines 3-5, 19-33). Therefore the claimed invention of claims 1-5 and 11-13 are anticipated by the reference of Lichter et al.

Regarding claim 8 and 9, Lichter et al. teach wherein the probe comprises a detectable label wherein the label is a florescent label (page 4, lines 21-25 and page 12, lines 11-21). Therefore the claimed invention of claims 8 and 9 are anticipated by the reference of Lichter et al.

Claim Rejections - 35 USC § 102(e)

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the Applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the Applicant for patent.

11. Claims 1-5 and 11-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Sinnett et al. (US 6, 183,963 B1, filed October 1998). Regarding claims 1-5 and 11-13, Sinnett et al. teach a DNA nucleic acid sequence about 17-25 nucleotides in length that specifically binds under selective conditions to a nucleic acid sequence comprising at least one variance in a gene of the Cytochrome P450 (CYP3A4) gene) or a sequence complementary thereto and/or isolated DNA nucleic acid sequence of about 17-25 nucleotides in length comprising at least one variance of the CYP3A4 gene) (page 4, lines 21-25 and page 5, lines 3-5, 19-33). Therefore the claimed invention of claims 1-5 and 11-13 are anticipated by the reference of Sinnett et al.

12. Claims 1-7, 11-13 are rejected under 35 U.S.C. 102(e) as being anticipated by Housman et al. (6,200,754 B1, filed March 1998). Regarding claim 1, Housman et al. teach a nucleic acid comprising a nucleic acid sequence at least 12 to 30 nucleotides in length that specifically binds under selective binding conditions to a nucleic acid sequence comprising at least one variance or sequence complementary thereto of a conditionally essential gene wherein one of the conditionally

essential genes is CYP3A4 (col. 7, lines 28-53 and Table 2. *See also claims 2 and 3.*). Therefore the claimed invention of claim 1 is anticipated by the reference of Housman et al.

Claim 2-4 are drawn to an embodiment of claim 1 wherein said probe comprises a nucleic acid sequence 200 nucleotide bases or fewer in length (clm 2) or 100 or fewer nucleotide bases in length (clm 3) or 25 or fewer nucleotide bases in length (clm 3). Housman et al. teach this embodiment (col. 7, lines 28-53).

Claim 5-7 are drawn to an embodiment of claim 1, wherein said probe comprises DNA(clm 5) or DNA and at least one nucleic acid analog (clm 6) or peptide nucleic acid (PNA) (clm 7). Housman et al. teach wherein the probe is DNA and may comprises a nucleic acid analog or may comprises of a peptide nucleic acid (col. 15, lines 7-66 and col. 16, lines 40-67).

Claims 11-13 are drawn to an isolated, purified or enriched nucleic acid sequence of 15 to 500 nucleotides in length (clm 11) or 15 to 100 nucleotide bases in length (clm 12) or 15 to 25 nucleotide bases in length (clm 13), comprising at least one variance, wherein said sequence has the base sequence of a portion of an allele of a Cytochrome P-450 gene (CYP3A4) or sequence complementary thereto or RNA equivalent. Housman et al. teach this embodiment (col. 7, lines 32-45 and col. 15, lines 19-21).

The claimed invention of claims 1-7 and 11-13 are anticipated by the reference of Housman et al.

Conclusion

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cynthia Wilder whose telephone number is (703) 305-1680. The examiner can normally be reached on Monday through Thursday from 7:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152. The official fax phone number for the Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed the Group's receptionist whose telephone number is (703) 308-0196.

Cynthia B. Wilder

Cynthia B. Wilder, Ph.D.

August 24, 2001

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600

6/27/01